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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 172

[Docket No. 02F–0160]

Food Additives Permitted for Direct Addition to Food for Human Consumption; Vitamin D_3

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of vitamin D_3 as a nutrient supplement in calcium-fortified fruit juices and juice drinks, excluding fruit juices and juice drinks specially formulated or processed for infants, at levels not to exceed 100 International Units (IU) per reference amount customarily consumed (RACC). This action is in response to a petition filed by The Minute Maid Co.

DATES: This rule is effective [*insert date of publication in the* **Federal Register**]. Submit written objections and requests for a hearing by [*insert date 30 days after date of publication in the* **Federal Register**]. The Director of the Office of the **Federal Register** approves the incorporation by reference of certain publications in § 172.380 (21 CFR 172.380) as of [*insert date of publication in the* **Federal Register**].

ADDRESSES: Submit written objections and requests for a hearing to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers

02F-0160

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Lane, rm. 1061, Rockville, MD 20852. Submit electronic objections to http://www.fda.gov/dockets/ecomments.

FOR FURTHER INFORMATION CONTACT: Judith L. Kidwell, Center for Food Safety and Applied Nutrition (HFS–265), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 202–418–3354.

SUPPLEMENTARY INFORMATION:

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I. Introduction

In a notice published in the **Federal Register** of April 25, 2002 (67 FR 20533), FDA announced that a food additive petition (FAP 2A4734) had been filed by The Minute Maid Co., c/o King and Spalding, 1700 Pennsylvania Ave. NW., Washington, DC 20006. The petition proposed that the food additive regulations be amended in 21 CFR part 172 to provide for the safe use of

vitamin D_3 in calcium-fortified fruit juices and juice drinks at levels not to exceed 100 IU per RACC[1].

Vitamin D[2] is affirmed as generally recognized as safe (GRAS) in § 184.1950(c)(1) (21 CFR 184.1950(c)(1)), in accordance with 21 CFR 184.1(b)(2), for use as a nutrient supplement, as defined in 21 CFR 170.3(o)(20), as the sole source of added Vitamin D in foods within the limitations specified in the following table:

TABLE 1.

Category of Food	Maximum Levels in Food (As Served)
Breakfast cereals	350 IU/100 grams (g)
Grain products and pastas	90 IU/100 g
Milk	42 IU/100 g
Milk products	89 IU/100 g

Additionally, vitamin D is affirmed as GRAS for use in infant formula (§ 184.1950(c)(2)) and as an optional ingredient in margarine (§ 184.1950(c)(3)).

Vitamin D is essential for human health. Humans can synthesize significant amounts of vitamin D_3 in skin from its precursor, 7-dehydrocholesterol, under exposure to ultraviolet B radiation in sunlight. Other sources of naturally occurring vitamin D are foods such as butter, buttermilk, cheese, cream, eggs, fish, goat milk, meat fats and organ meats, mushrooms, and sour cream.

The major function of vitamin D is the maintenance of blood serum concentrations of calcium and phosphorus by enhancing the absorption of these minerals in the small intestine. Vitamin D deficiency can lead to abnormalities in calcium and bone metabolism such as rickets in children or

[1]RACC values represent the amount of food typically consumed per eating occasion. The RACC for fruit juices and juice drinks intended for the general population is 240 milliliters (mL) (21 CFR 101.12).

[2]Vitamin D comprises a group of fat soluble seco-sterols and comes in many forms. The two major physiologically relevant forms are vitamin D_2 and vitamin D_3. Vitamin D without a subscript represents either D_2 or D_3. As used in § 184.1950, the meaning of the term vitamin D includes crystalline vitamin D_2, crystalline vitamin D_3 and vitamin D_2 resin, and vitamin D_3 resin.

osteomalacia in adults. The elderly, who have significantly decreased capacity for the production of vitamin D_3 in skin, and patients with intestinal malabsorption syndromes are especially prone to vitamin D deficiency. At high levels, vitamin D may be toxic. Because it is metabolized to inactive forms in the skin, vitamin D does not accumulate significantly in the body as a result of sun exposure. Excessive dietary intake of vitamin D elevates blood plasma calcium levels by increased intestinal absorption and/or mobilization from the bone.

Vitamin D_3, also known as cholecalciferol, is the chemical 9,10-seco(5Z,7E)-5,7,10(19)-cholestatrien-3-ol. Vitamin D_3 occurs in, and is isolated from fish liver oils. It also is manufactured by ultraviolet irradiation of 7-dehydrocholesterol that is derived synthetically from natural cholesterol. In both methods, vitamin D_3 is purified by crystallization.

To support the safety of the proposed use of vitamin D_3, The Minute Maid Co. submitted a summary of the metabolism of vitamin D, a number of publications pertaining to human clinical studies, bioavailability studies, and dietary intake estimates. Based on these data, the petitioner concludes that the proposed use of vitamin D_3 in calcium-fortified fruit juices and juice drinks is safe.

II. Evaluation of Safety

In order to establish, with reasonable certainty, that a new food additive is not harmful under its intended conditions of use, FDA considers the projected human dietary exposure to the additive, the additive's toxicological data, and other relevant information (such as published literature) available to the agency.

In determining whether the proposed use of an additive is safe, FDA compares an individual's estimated daily intake (EDI) of the additive to an acceptable intake level established by toxicological data. The EDI is determined by projections based on the amount of the additive proposed for use in particular foods and on data regarding the consumption levels of these particular foods. The agency commonly uses the EDI for the 90th percentile consumer of a food additive as a measure of high chronic dietary exposure.

A. Acceptable Daily Intake for Vitamin D for Adults, Children, and Infants

In 1997, the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board at the National Academy of Sciences Institute of Medicine (IOM) conducted an extensive review of toxicology and metabolism studies on vitamin D published through 1996. The IOM published a detailed report that included a tolerable upper intake level (UL) for vitamin D (both D_2 and D_3) for infants, children and adults (Ref. 1). The IOM UL for vitamin D for children 1 to 18 years of age and adults is 2,000 IU/day and for infants is 1,000 IU/day.

The IOM considers the UL as the highest usual intake level of a nutrient that poses no risk of adverse effects when the nutrient is consumed over long periods of time. The UL is determined using a risk assessment model developed specifically for nutrients and considers intake from all sources: Food, water, nutrient supplements, and pharmacological agents. The dose-response assessment, which concludes with an estimate of the UL, is built upon three toxicological concepts commonly used in assessing the risk of exposures to chemical substances: No observed adverse effect level, lowest observed effect level and an uncertainty factor.

B. Estimated Daily Intake for Vitamin D

The petitioner provided average and 90th percentile vitamin D intake estimates for consumers of fruit juices and juice drinks from: (1) The proposed use in calcium-fortified fruit juices and juice drinks, (2) current uses in conventional foods (including naturally occurring sources of vitamin D), (3) current and proposed uses in conventional foods, and (4) current and proposed uses in both conventional foods and dietary supplements. The petitioner presented intake estimates for the general population, 2 years of age and older, and for 15 population subgroups (including estimates for infants less than 1 year old; children 1 year to 3 years old; and adults). The agency has determined that the methodology used to calculate these estimates is appropriate (Ref. 2).

For the proposed food use, dietary intake of vitamin D_3 for 90th percentile consumers of fruit juices and juice drinks, 2 years of age and older, was estimated to be 211 IU per person per day (IU/p/d). The corresponding mean intake was estimated to be 110 IU/p/d.

For currently regulated uses in conventional foods (including naturally occurring sources), mean dietary exposure to vitamin D for consumers of fruit juices and juice drinks was estimated to be 197 IU/p/d for consumers 2 years of age and older. Intake at the 90th percentile was estimated to be 368 IU/p/day. For consumers of fruit juices and juice drinks 2 years of age and older, average and 90th percentile dietary intakes from current (including naturally occurring sources) and proposed food uses of vitamin D were estimated to be 306 IU/p/d and 519 IU/p/d, respectively.

The petitioner also considered the intake of vitamin D from dietary supplements. The National Health and Nutrition Examination Survey III (NHANES III) data indicate that approximately 40 percent of the U.S.

population 2 months of age and older take dietary supplements. The NHANES III data also show that, when vitamin D is taken as a dietary supplement, the most frequent level is 400 IU/day. The petitioner provided results from two Gallup polls that concluded that consumers of vitamin D_3-fortified fruit juices and fruit drinks also are likely to take supplemental sources of vitamin D. As a conservative estimate of intake of vitamin D from dietary supplements and food uses, the petitioner assumed that all consumers of fruit juices and juice drinks would take dietary supplements containing 400 IU of vitamin D. They then added this value to the mean and 90th percentile intake estimates from current and proposed food uses. For consumers of fruit juices and juice drinks 2 years of age and older, mean and 90th percentile dietary intake estimates from current and proposed food uses and dietary supplements were 706 IU/p/d and 919 IU/p/d, respectively.

Although the petitioner has notified FDA that it does not intend to fortify fruit juices and juice drinks specially formulated or processed for infants with vitamin D_3, the petitioner provided intake estimates for breastfed and non-breastfed infants, 0 to 6 months of age and 7 to 12 months of age. These estimates assumed that all fruit juices and juice drinks, including those specially formulated or processed for infants, would be fortified with vitamin D_3. Of these four infant population groups, intake estimates were the highest for non-breastfed infants, 0 to 6 months of age. For non-breastfed infants, 0 to 6 months of age, mean and 90th percentile dietary intake from current and proposed food uses were 443 IU/p/d and 663 IU/p/d, respectively. When dietary supplements were considered in the estimates for these consumers, mean and 90th percentile intakes were 843 IU/p/d and 1,063 IU/p/d,

respectively. Intake estimates for the other infant population groups were below the UL for infants of 1,000 IU/day.

Due to the relatively small sample size of infants consuming fruit juices and juice drinks, the agency does not consider the intake estimates presented by the petitioner to be statistically robust enough to make a quantitative safety assessment. For example, for infants 0 to 6 months of age, non-breastfed, intake estimates were based on data from 49 consumers of fruit juice or juice drinks; for infants, 0 to 6 months, breastfed, 16 consumers; infants, 7 to 12 months, non-breastfed, 75 consumers; and infants, 7 to 12 months, breastfed, 9 consumers. Intake estimates from these populations are not considered to be statistically robust when compared, for example, to the numbers of consumers in the sample populations for children 4 to 8 years of age (1,194 consumers) and 9 to 13 years of age (717 consumers).

Because a quantitative safety assessment cannot be made with the available data, we consider it appropriate to exclude fruit juices and juice drinks specially formulated or processed for infants (ages 0 to 12 months) from the proposed use of vitamin D_3. The agency recognizes that some infants may consume fruit juices and juice drinks that are not specially formulated or processed for infants (Ref. 3); however, fruit juices and juice drinks are not major components of the diets of infants. Further, in a May 2001 policy statement, the American Academy of Pediatrics recommended that fruit juice should not be given to infants before 6 months of age (Ref. 4).

C. Safety Assessment

The petitioner submitted over 80 published articles to support the safety of the proposed use of vitamin D_3 in calcium-fortified fruit juices and juice drinks. These articles included most of the references considered by IOM in

its evaluation and all of the critical references that were the basis for the UL. The petitioner also submitted publications on vitamin D that appeared in the literature subsequent to the 1997 IOM report. New information since 1997 supports that vitamin D intake is without adverse effects at the IOM UL for adults (Ref. 5). No new studies in children on the effects of vitamin D intake have been published since 1997.

We considered the UL established by IOM for children (ages 1 year and older) and adults relative to the intake estimates provided by the petitioner as the primary basis for assessing the safety of the proposed use of vitamin D_3 in calcium-fortified fruit juices and juice drinks. For all population groups of children and adults evaluated, mean and 90th percentile intake estimates from current and proposed food uses of vitamin D are well below the IOM UL of 2,000 IU/p/day. Additionally, when dietary supplements are included in the calculations, intake estimates remain below the UL. Because the EDI of vitamin D from all sources is less than the UL, the agency believes that dietary exposure of vitamin D_3 from its use as a nutrient supplement in calcium-fortified fruit juices and juice drinks, excluding juices and juice drinks specially formulated or processed for infants, will not pose a safety concern (Ref. 5)

III. Conclusion

Based on all data relevant to vitamin D reviewed by the agency, FDA concludes that there is a reasonable certainty that no harm will result from the use of vitamin D_3 as a nutrient supplement at the levels specified in calcium-fortified fruit juices and juice drinks, excluding fruit juices and juice drinks specially formulated or processed for infants. Thus, vitamin D_3 is safe for its proposed use and the agency concludes that the food additive

regulations should be amended as set forth in this document. To ensure that only food grade vitamin D_3 is used in food, the additive must meet the specifications of the *Food Chemicals Codex*, 4th ed.

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition by appointment with the information contact person listed previously. As provided in § 171.1(h), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

IV. Environmental Effects

The agency has previously considered the environmental effects of this rule as announced in the notice of filing for FAP 2A4734 (67 FR 20533). No new information or comments have been received that would affect the agency's previous determination that there is no significant impact on the human environment and that an environmental impact statement is not required.

V. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VI. References

The following references have been placed on display in the Dockets Management Branch (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, "Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride," National Academy Press, Washington, DC, 1997.

2. Memorandum from Folmer, Division of Petition Review, Chemistry Review Group, to Kidwell, Division of Petition Review, May 21, 2002.

3. Meeting minutes from August 2 and August 28, 2002, Internal meetings, Division of Petition Review.

4. American Academy of Pediatrics Policy Statement "The Use and Misuse of Fruit Juice in Pediatrics (RE0047)," *Pediatrics*, 107(5): 1210–1213, 2001.

5. Memorandum from Park, Division of Petition Review, Toxicology Review Group, to Kidwell, Division of Petition Review, September 17, 2002.

VII. Objections

Any person who will be adversely affected by this regulation may at any time file with the Dockets Management Branch (see **ADDRESSES**) written or electronic objections. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and

analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents are to be submitted and are to be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 172

Food additives, Incorporation by reference, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 172 is amended as follows:

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

1. The authority citation for 21 CFR part 172 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 348, 371, 379e.

2. Section 172.380 is added to subpart D to read as follows:

§ 172.380 Vitamin D_3.

The food additive may be used safely in foods as a nutrient supplement defined under § 170.3(o)(20) of this chapter in accordance with the following prescribed conditions:

(a) Vitamin D_3, also known as cholecalciferol, is the chemical 9,10-seco(5Z,7E)-5,7,10(19)-cholestatrien-3-ol. Vitamin D_3 occurs in and is isolated

from fish liver oils. It also is manufactured by ultraviolet irradiation of 7-dehydrocholesterol produced from cholesterol and is purified by crystallization.

(b) Vitamin D_3 meets the specifications of the *Food Chemicals Codex*, 4th ed. (1996), p. 434, which is incorporated by reference. The Director of the Office of the Federal Register approves this incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. You may obtain copies from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418 (Internet address http://www.nap.edu/. Copies may be examined at the Center for Food Safety and Applied Nutrition's Library, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(c) Vitamin D_3 may be added, at levels not to exceed 100 International Units (IU) per serving, to 100 percent fruit juices, as defined under § 170.3(n)(35) of this chapter, excluding fruit juices that are specially formulated or processed for infants, that are fortified with greater than 33 percent of the Recommended Daily Intake (RDI) of calcium per Reference Amount Customarily Consumed (RACC).

(d) Vitamin D_3 may be added, at levels not to exceed 100 IU per serving, to fruit drinks, as defined under § 170.3(n)(35) of this chapter, excluding fruit drinks that are specially formulated or processed for infants, that are fortified with greater than 10 percent of the RDI of calcium per RACC.

Dated: February 21, 2003.
February 21, 2003.

William K. Hubbard,
Associate Commissioner for Policy and Planning.

[FR Doc. 03–????? Filed ??–??–03; 8:45 am]

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